

Huang, X., Kalladka, D., Cheripelli, B. K., Moreton, F. C. and Muir, K. W. (2017) The impact of CT perfusion threshold on predicted viable and nonviable tissue volumes in acute ischaemic stroke. *Journal of Neuroimaging*, 27(6), pp. 602-606.

There may be differences between this version and the published version. You are advised to consult the publisher's version if you wish to cite from it.

Huang, X., Kalladka, D., Cheripelli, B. K., Moreton, F. C. and Muir, K. W. (2017) The impact of CT perfusion threshold on predicted viable and nonviable tissue volumes in acute ischaemic stroke. *Journal of Neuroimaging*, 27(6), pp. 602-606. (doi:[10.1111/jon.12442](https://doi.org/10.1111/jon.12442))

This article may be used for non-commercial purposes in accordance with [Wiley Terms and Conditions for Self-Archiving](#).

<http://eprints.gla.ac.uk/138199/>

Deposited on: 13 March 2017

# The impact of CT Perfusion Threshold on Predicted Viable and Non-viable Tissue Volumes in Acute ischaemic stroke

Xuya Huang<sup>1</sup> PhD, MRCP, Dheeraj Kalladka<sup>1</sup> MRCP, Bharath Kumar Cheripelli<sup>1</sup> MRCP, Fiona Catherine Moreton<sup>1</sup> PhD, MRCP, Keith W Muir<sup>1</sup> MD, FRCP

<sup>1</sup> Institute of Neuroscience and Psychology, University of Glasgow, Queen Elizabeth University Hospital, United Kingdom

Running title: Different tissue definitions lead to variable tissue volume

Correspondence to: Prof Keith Muir, Institute of Neuroscience & Psychology, University of Glasgow, Queen Elizabeth University Hospital, Glasgow G51 4TF, Scotland, UK

Tel (+44)0141 451 5892

Email: keith.muir@glasgow.ac.uk

Keywords: Perfusion imaging, Patient selection, Reperfusion, outcome

Acknowledgement: This study is funded by the Stroke association (TSA2010/04).

Disclosure: None

## Abstract

**Background and purpose:** Perfusion imaging is used for patient selection in clinical practice and trials. Post-processing and definitions of tissue viability are nevertheless not standardised. We compared the lesion volumes generated with two well-recognised perfusion tissue definitions in a single centre phase two thrombolysis study.

**Methods:** We analysed perfusion imaging data from the Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST) study using two popular tissue viability thresholds (ischaemic core definition: 1) cerebral blood volume  $<2.0\text{mL}/100\text{g}^{-1}$  or 2) relative cerebral blood flow  $<40\%$  that of the contralesional hemisphere and relative delay time  $>2$  seconds; penumbra definitions: 1) Mean Transit Time  $>145\%$  of contralesional hemisphere or 2) relative Delay Time  $<2$  seconds). We compared volumes of core and penumbra, mismatch ratio, percentage and volume of penumbra salvaged at 24 hours.

**Results:** We included 73 (Tenecteplase= 36, Alteplase=37) patients who had analysable perfusion lesions at baseline. Significant differences were found in core volumes using the two thresholds ( $33\pm37\text{mL}$  versus  $26\pm32\text{mL}$ ,  $p<0.001$ ), as was mismatch ratio ( $2.5\pm0.9$  versus  $4.2\pm3.7$ ,  $p<0.001$ ). The volume of penumbra salvaged at 24 hours ( $30\pm19\text{mL}$  versus  $35\pm26\text{mL}$ ,  $p=0.043$ ) differed significantly, although the percentages of penumbra salvaged did not ( $p=0.2$ ). No difference was found between the two thrombolytic agents in the percentages of penumbra salvaged using either threshold.

**Conclusion:** Two commonly used tissue definitions generated significantly different lesion volumes, and mismatch ratios. Threshold selection may have significant impact on patient selection for trials or reperfusion therapies.

## **Introduction**

Computed tomography perfusion (CTP) imaging has been used widely in both clinical and research settings to select candidates for reperfusion therapy, or as a biomarker for efficacy and safety. There is no consensus regarding the most accurate thresholds that define ischaemic core or penumbral tissue, however, literature-reported viability thresholds were derived using a variety of methods, some based on very small numbers of cases,<sup>1</sup> and implementation on commercial software varies.

We aimed to compare the lesion volumes generated by two commonly used viability thresholds,<sup>2,3</sup> and explored potential impact on patient selection.

## **Methods**

We used the imaging data from the Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST) trial that compared the efficacy and safety of alteplase and tenecteplase as thrombolytic agents in acute ischaemic stroke, in which imaging variables were the primary outcome but patients were not selected on the basis of imaging criteria. The study protocol of ATTEST has been detailed elsewhere.<sup>4</sup> Briefly, eligible thrombolysis candidates within 4.5h of onset were randomised to receive alteplase (0.9mg/kg to a maximum 90mg) or 0.25mg/kg tenecteplase (to a maximum 25mg). Baseline imaging comprised non-contrast CT (NCCT), CT perfusion (CTP) and CT angiography (CTA). CTP and CTA were undertaken either before or immediately following the thrombolysis bolus to avoid treatment delay. Follow-up imaging including NCCT and CTA was carried out between 24 and 48 hours post-thrombolysis.

All scans were performed on a Philips Brilliance 64 multidetector scanner. Whole brain NCCT was acquired first, (5 mm slice thickness FOV 218 x 218 mm, 120 kv, 171 mA or 0.9 mm slice thickness, FOV 250x250 mm, 120 kV, 404 mA) followed by CTP with 40 mm slab coverage from the basal ganglia (8x5 mm slices, FOV 25 cm, 80 kVp, 476 mA, 2 second cycle time, 30 cycles) using a 50 ml contrast bolus administered at 5 mls per second (350 Xenetix) via a large-gauge cannula. A CTA covering aortic arch to the top of the lateral ventricles (0.67 mm slice thickness, 120 kV, 475 mA) was acquired during the first arterial past of contrast (Xenetix 350, 60 mls, followed by 30 mls of saline bolus, both given at 5 ml per second). Follow-up CTA covered from base of skull to the top of lateral ventricles.

The detailed post-processing and imaging analysis methods were described in the main study.<sup>4</sup> In summary, CTP was processed offline with MISTar (Apollo Medical Imaging Technology, Melbourne, VIC, Australia), which uses a delay-corrected single value decomposition (SVD) deconvolution algorithm.

We used the following definitions:

- Penumbra volume salvaged = penumbra volume on baseline CTP – penumbra volume that infarcted on 24h NCCT;
- Percentage of penumbra salvaged = (penumbra salvage/penumbra Volume) x 100

We compared two tissue viability thresholds:

- Wintermark's definition (MW):<sup>2</sup> Irreversible tissue – tissue with reduced Cerebral Blood Volume (CBV) <2.0mL/100g; Viable tissue – tissue with relative Mean Transit Time (MTT) >145% of contralesional hemisphere and CBV >2.0ml/100g.

- Bivard's definition (AB):<sup>3</sup> Irreversible tissue – tissue with reduced CBF (relative CBF < 40% that of the contralesional hemisphere) and prolonged Delayed Time (DT) (relative DT >2 seconds); Viable tissue – tissue with relative DT>2 seconds and rCBF>40%.

All imaging studies were analysed by two research fellows (XH and BC) twice independently with an interval of 4 weeks between processing, and blind to CTA findings. Inter-rater agreements were evaluated. For baseline irreversible tissue volume, the intra-class correlation coefficient was 0.96 (95% limits of agreement -16-20mL). For penumbra volumes, the correlation coefficient was 0.91 with 95% limits of agreement of -30-30mL. The average of four readings was taken as the final reading for analysis.

Values were expressed as mean and standard deviation (SD) or median and interquartile range (IQR) depending on normal distribution or not. Paired T tests and related-samples Wilcoxon Signed rank tests were used to compare the results produced by the two definitions. The differences in the percentage or volume of penumbra salvaged between the two treatment groups were compared with independent samples T tests. Statistical analyses were performed with IBM SPSS statistics (SPSS Chicago, Illinois, USA v.19) and StatsDirect 2.8.

## Results

Among the 104 participants in the ATTEST study, 73 (mean age [SD] 73 [11] years; median baseline NIHSS [IQR] 13 [9-19]) had measureable perfusion lesions, of whom 36 received tenecteplase, and 37 alteplase, at a mean (SD) 189 (46) minutes from symptoms onset. 69 out of 73 (93.5%) patients had occlusion on baseline CTA.

Table 1 shows the differences between the lesion volumes measured with two thresholds, core/penumbra mismatch ratio, the volume and percentage of penumbra salvaged at 24 hours. There was a systematic difference in core and penumbra volume estimates with the AB method estimating a smaller core and a larger penumbra compared to the MW thresholds (Figure 1). The mean differences of the volume and percentage of penumbra salvaged at 24 hours between the alteplase and tenecteplase treated groups using two thresholds were not different.

The numbers with different “mismatch” ratios did not differ significantly between the two thresholds. The effects of applying different patient selection criteria from recent clinical trials including core:penumbra ratio, vessel occlusion and core volume are shown in Figure 2. Differences in eligibility between the two thresholds ranged from 0% to 43% depending upon criteria.

## **Discussion**

We observed that different CTP tissue viability thresholds led to significantly different estimates of core volume and mismatch ratio. There was no difference in penumbra salvage at 24h using the two thresholds, however.

Despite increasing clinical use, perfusion imaging analysis is not standardised, with variability in post-processing algorithms,<sup>5,6</sup> and various combinations of perfusion parameters and thresholds to define core and penumbral tissue.<sup>7</sup> The principal purpose of defining tissue viability by perfusion imaging is to better estimate the risk:benefit balance for reperfusion treatments. Baseline ischaemic core and penumbra volumes correlate with clinical outcome after intravenous thrombolysis,<sup>8,9</sup> and the presence of a “large core” in particular signifies higher risk of both intracerebral haemorrhage and significant brain



oedema.<sup>10</sup> Observational data suggest that intravenous thrombolysis <4.5h after onset<sup>11</sup> or late endovascular reperfusion<sup>12</sup> are not beneficial in the absence of a “target mismatch” pattern, defined as presence of a minimum penumbra volume and ratio of penumbra:core. Operational definitions of penumbra and core may thus be important for appropriate treatment decisions, but a single definition of what thresholds constitute the most reliable estimates of tissue viability may not be possible, as these may depend on the factors noted below.

Comparison of six commonly used post-processing software and different tissue definitions<sup>13</sup> concluded that Bivard’s threshold with delay-corrected SVD algorithm was the most accurate among several used in currently available post-processing algorithms. Optimal thresholds may differ due to factors other than the post-processing algorithm, however, and may depend on other factors that have not been investigated systematically including the time window for treatment, the specific treatment intervention, and the speed of reperfusion.

Several multicentre reperfusion studies<sup>4,14-20</sup> used perfusion biomarkers to select patients. Variability in thresholds applied by both commercial software and in centres may lead to variation in patient selection, even with clear imaging selection criteria. Such variation may have contributed to the lack of apparent treatment effect in the DIAS-2 trial of desmoteplase,<sup>18</sup> and reclassification of patients is common when comparing clinician interpretation and automated “core lab” processing.<sup>11</sup> Recent endovascular reperfusion trials that used CTP penumbral selection applied different criteria for “target mismatch” although the same post-processing software was employed. The implications of variability in these criteria on patient selection are illustrated in Figure 2.

Additional acquisition and processing time for multimodal CT assessment may delay administration of thrombolytic treatment, with typical average times for acquisition of multimodal imaging<sup>21</sup> of 15 minutes. Whether the potential reduction in benefit resulting from this delay is mitigated by improved patient selection and consequently better outcomes within the 4.5h time window is under investigation in the ongoing Penumbra and Recanalisation Acute Computed Tomography in Ischaemic Stroke Evaluation (PRACTISE) trial.<sup>22</sup>

We evaluated only the effect of different perfusion thresholds since other aspects of post-processing were identical. Multi-centre experience using different equipment and software analysis methods will almost certainly be more variable. Several studies have suggested that thresholded CBF is more accurate in defining irreversible tissue.<sup>23-25</sup> However, some commercial software still uses CBV to define infarct core. In addition to the modest sample size, our study has several limitations. The algorithm used in MISTar is a modified SVD with compensation for the effects of arterial delay and dispersion,<sup>26</sup> whereas the MW thresholds were derived with software based on the central volume principle.<sup>2</sup> It is possible that MISTar is not optimised to process perfusion imaging using the MW definition, as it is not configured to allow direct thresholding of core tissue based on cerebral blood volume.<sup>13</sup> Our analysis was carried out prior to a recent report that tissue with  $rDT > 3s$  more closely corresponds to penumbra than  $rDT > 2s$ .<sup>11</sup>, which may affect our results. Longer acquisition times for CTP than were employed in our study may more fully characterise the time:attenuation curve, reducing the risk of truncation of the contrast bolus that may occur with low cardiac output states, and improving reliability of CBV and CBF estimation. Other technical limitations include using CT to measure final infarct volume, as 24 hours post thrombolysis, the infarcted tissue is still poorly defined; and the limited z-axis coverage of CT perfusion of 4cm.

## **Conclusion**

Different viability thresholds alone can generate significantly different core volume estimates leading to variable mismatch ratio. Clinicians need to consider standardised definitions and processing in multicentre studies.

## References

1. Dani AK, Thomas RGR, Chappell FM, et al. Computed tomography and magnetic resonance perfusion imaging in ischemic stroke: Definitions and thresholds. *Annals of neurology* 2011;70:384-401.
2. Wintermark M, Flanders AE, Velthuis B, et al. Perfusion-CT Assessment of Infarct Core and Penumbra : Receiver Operating Characteristic Curve Analysis in 130 Patients Suspected of Acute Hemispheric Stroke. *Stroke* 2006;37:979-85.
3. Bivard A, Spratt N, Levi C, Parsons M. Perfusion computer tomography: Imaging and clinical validation in acute ischaemic stroke. *Brain : a journal of neurology* 2011;134:3408-16.
4. Huang X, Cheripelli BK, Lloyd SM, et al. Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded endpoint study. *Lancet neurology* 2015;14:368-76.
5. Kudo K, Sasaki M, Yamada K, et al. Difference in CT Perfusion maps generated by different commercial software: Quantitative analysis by using identical source data of acute stroke patients. *Radiology* 2010;254:200-9.
6. Kudo K, Christensen S, Sasaki M, et al. Accuracy and Reliability Assessment of CT and MR Perfusion Analysis Software Using a Digital Phantom. *Radiology* 2013;267:201-11.
7. Warach SJ, Luby M, Albers GW, et al. Acute Stroke Imaging Research Roadmap III Imaging Selection and Outcomes in Acute Stroke Reperfusion Clinical Trials: Consensus Recommendations and Further Research Priorities. *Stroke* 2016;47:1389-98.
8. Konzas AA, Wintermark M, Lev MH. CT perfusion imaging in acute ischaemic stroke. *Neuroimaging clinics of North America* 2011;21:215-38.
9. Zhu G, Michel P, Aghaebrahim A, et al. Computed tomography workup of patients suspected of acute ischemic stroke: perfusion computed tomography adds value compared

with clinical evaluation, noncontrast computed tomography, and computed tomography angiogram in terms of predicting outcome. *Stroke* 2013;44:1049-55.

10. Cheripelli BK, Huang X, MacIsaac R, Muir KW. Interaction of Recanalization, Intracerebral Hemorrhage, and Cerebral Edema After Intravenous Thrombolysis. *Stroke* 2016;47:1761-7.
11. Bivard A, Levi C, Krishnamurthy V, et al. Perfusion computed tomography to assist decision making for stroke thrombolysis. *Brain* 2015;138:1919-31.
12. Lansberg MG, Straka M, Kemp S, et al. MRI profile and response to endovascular reperfusion after stroke (DEFUSE 2): a prospective cohort study. *Lancet Neurol* 2012;11:860-7.
13. Bivard A, Levi C, Spratt N, Parsons M. Perfusion CT in Acute Stroke: Comprehensive Analysis of Infarct and Penumbra. *Radiology* 2013;267:543-50.
14. Parsons MW, Spratt N, Bivard A, et al. A randomised trial of tenecteplase versus alteplase for acute ischaemic stroke. *New England Journal of Medicine* 2012;366:1099-107.
15. Campbell BCV, Mitchell PJ, Kleinig TJ, et al. Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection. *New England Journal of Medicine* 2015;372:1009-18.
16. Kidwell C, Jahan R, Gornbein J, et al. A Trial of Imaging Selection and Endovascular Treatment for Ischemic Stroke. *New England Journal of Medicine* 2013;368:914-23.
17. Hacke W, Albers G, Al-Rawi Y, et al. The Desmoteplase in Acute Ischemic Stroke Trial (DIAS) A Phase II MRI-Based 9-Hour Window Acute Stroke Thrombolysis Trial With Intravenous Desmoteplase. *Stroke* 2005;36:66-73.
18. Hacke W, Furlan A, Al-Rawi Y, et al. Intravenous desmoteplase in patients with acute ischaemic stroke selected by MRI perfusion diffusion weighted imaging or perfusion CT

(DIAS-2): a prospective, randomised, double-blind, placebo-controlled study. *Lancet neurology* 2009;8:141-50.

19. Lansberg MG, Straka M, Kemp S, et al. MRI profile and response to endovascular reperfusion after stroke (DEFUSE 2): a prospective cohort study. *Lancet neurology* 2012;11:860-7.

20. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *The New England journal of medicine* 2015;372:2285-95.

21. McVerry F, Dani AK, Thomas RGR, et al. Short acquisition time for multimodal CT examination in acute stroke. *Cerebraovascular diseases* 2011;31 (Suppl 2):95.

22. El-Tawil S WJ, Ford I, Mair G, Robinson T, Kaira L, Muir, KW. Penumbra and re-canalization acute computed tomography in ischemic stroke evaluation: PRACTISE study protocol *International Journal of Stroke* 2017:In press.

23. Bivard A, McElduff P, Spratt N, Levi C, Parsons M. Defining the extent of irreversible brain ischemia using perfusion computed tomography. *Cerebraovascular diseases* 2011;31:238-45.

24. Campbell BCV, Christensen S, Levi CR, et al. Cerebral blood flow is the optimal CT perfusion parameter for assessing infarct core. *Stroke* 2011;42:3435-40.

25. Kamalian S, Kamalian S, Maas MB, et al. CT cerebral blood flow maps optimally correlate with admission diffusion-weighted imaging in acute stroke but thresholds vary by postprocessing platform. *Stroke* 2011;42:1923-8.

26. Yang Q, inventor Method and system of obtaining improved data in perfusion measurements 2005.

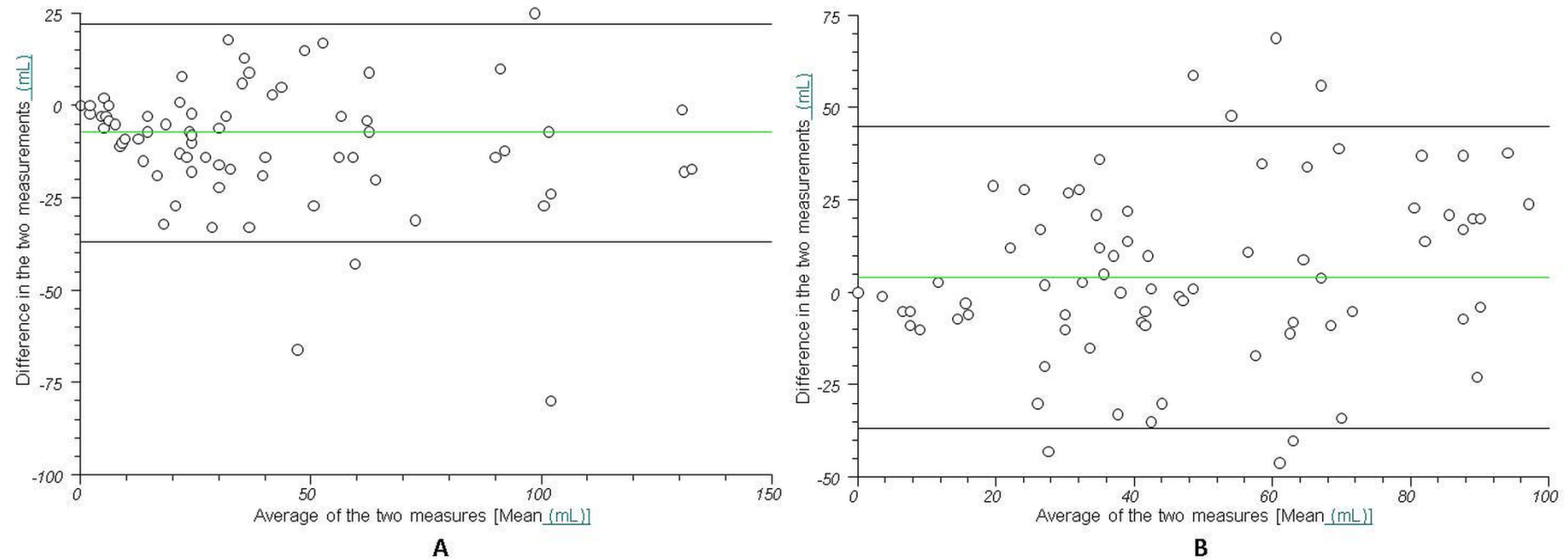
27. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. TIMI Study Group. *The New England journal of medicine* 1985;312:932-6.

28. Zaidat OO, Yoo AJ, Khatri P, et al. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. *Stroke* 2013;44:2650-63.

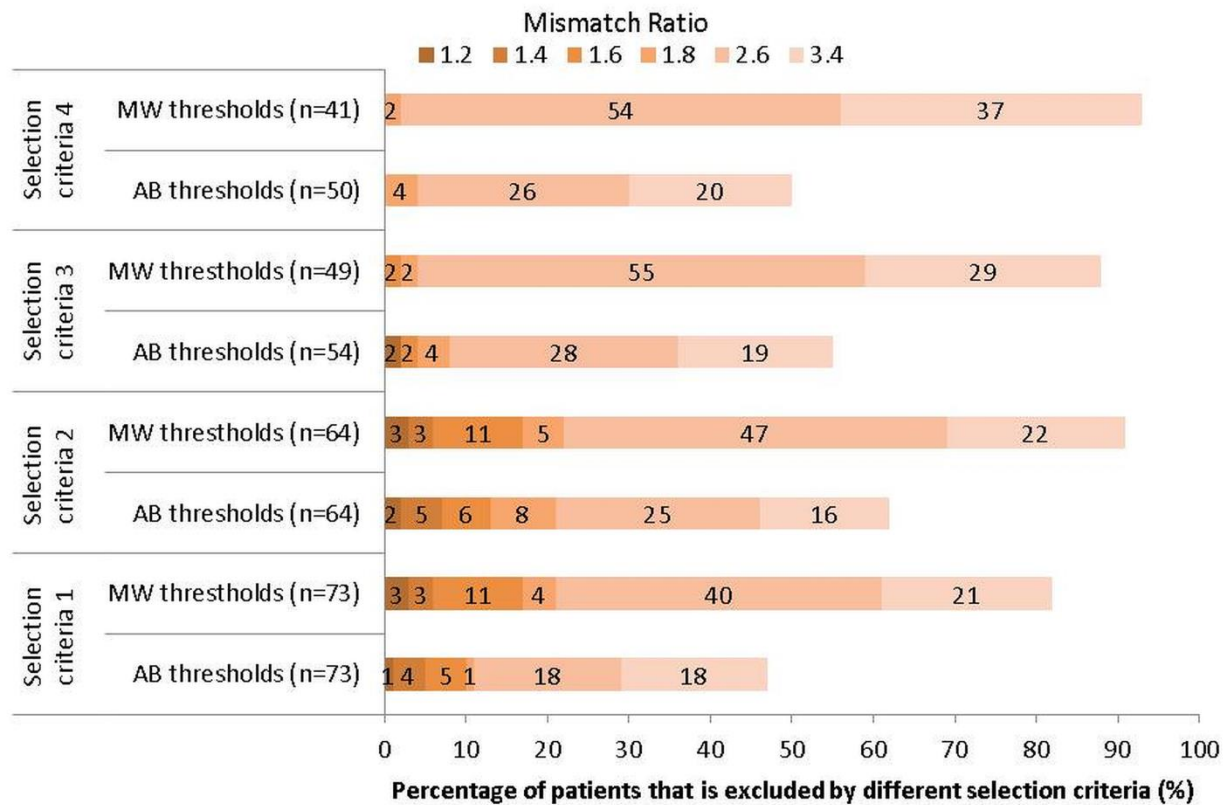
**Table 1. Differences of lesion size and penumbra salvaged between the measurements of the two tissue viability thresholds**

		AB definition <sup>3</sup>	MW definition <sup>2</sup>	Mean/Median Difference	P Value* (95%CI)
Ischaemic core mL	Mean (SD)	26 (32)	33 (37)	-10	<0.001 (-13.9– -6.1)
	Median (IQR)	14 (0–41)	25 (0–47)	-14	<0.001 (-20– -7.5)
Penumbra mL	Mean (SD)	51 (30)	45 (25)	5.5	0.058 (-0.2–11.1)
	Median (IQR)	46 (29–78)	42 (25–59)	5	0.091 (-1–11)
Volume of penumbra salvaged mL	Mean (SD)	35 (26)	30 (19)	4.7	0.043 (0.2–9.2)
	Median (IQR)	31 (13–49)	27 (14–44)	3.5	0.094 (-0.5–8)
Percentage of penumbra salvaged %	Mean (SD)	68 (25)	70 (25)	-2.1	0.2 (-5.4–1.1)
	Median (IQR)	75 (50–88)	78 (51–85)	-1.2	0.32 (-3.7–1)
Mismatch Ratio	Mean (SD)	4.2 (3.7)	2.5 (0.9)	1.7	<0.001 (0.9–2.5)
	Median (IQR)	2.9 (1.9–5)	2.3 (1.8–2.9)	1	<0.001 (0.6–1.6)
Recanalisation rate§ at 24–48 hours %	70% (44/63) [63 out of 73 patients had vessel occlusion on baseline CTA]				
AB=Bivard; MW=Wintermark; SD=Standard Deviation; IQR=Interquartile Range; CI=Confidence Interval; CTA= CT Angiography; * p-Value was calculated using paired T-tests for mean, and related-samples Wilcoxon Signed rank tests for median. § Recanalisation was defined as Thrombolysis in Myocardial Infarction (TIMI) 2–3. <sup>27,28</sup>					





**Figure 1. A. Inter-observer Bland-Altman 95% agreement plot for core volume between Bivard (AB) and Wintermark (MW) thresholds (mean[green] $\pm$ 1.96SD[black]). Intra-class correlation coefficient= 0.89; 95% limits of agreement (-36.9–22.1); B. Inter-observer Bland-Altman 95% agreement plot for penumbra volume between AB and MW thresholds. Intra-class correlation coefficient= 0.78; 95% limits of agreement (-37-45).**



- Figure 2. We applied four commonly used imaging selection criteria to the 73 patients. This graph shows the percentage of patients that is excluded by imaging selection using different criteria.** (Selection criteria 1: CT perfusion (CTP) mismatch ratio; Selection criteria 2: CTP mismatch ratio and large vessel occlusion [Internal carotid artery, M1(Middle cerebral artery from the

origin to bifurcation/trifurcation), M2 (from bifurcation to circular sulcus of insula) ]; Selection criteria 3: CTP mismatch ratio, large vessel occlusion and core volume <70mL; Selection criteria 4: CTP mismatch ratio, large vessel occlusion, core volume<70mL, and penumbra volume >20mL). **AB( Bivard) threshold: Irreversible tissue – tissue with reduced Cerebral Blood Flow (CBF) (relative CBF < 40% that of the contralesional hemisphere) and prolonged Delayed Time (DT) (relative DT >2 seconds); Viable tissue – tissue with relative DT>2 seconds and rCBF>40%; MW (Wintermark) threshold: Irreversible tissue – tissue with reduced Cerebral Blood Volume (CBV) <2.0mL/100g; Viable tissue – tissue with relative Mean Transit Time (MTT)>145% of contralesional hemisphere and CBV>2.0ml/100g.**